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IMAGING VIGNETTE

Pacemaker Therapy in Refractory Heart Failure

A Systematic Approach to Electromechanical Optimization of Diastolic Function

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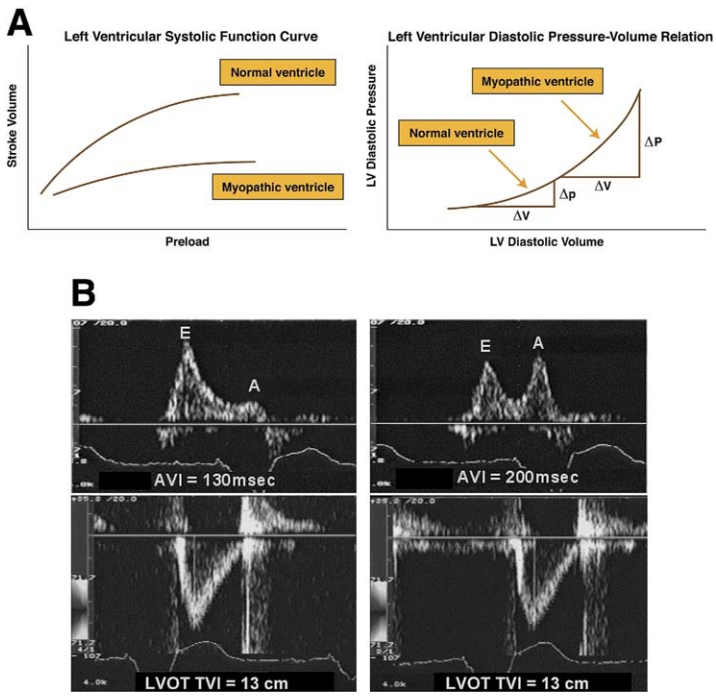
CARDIAC RESYNCHRONIZATION THERAPY (CRT) has been targeted primarily at improving left ventricular *systolic* function. Whereas the discordance rate between the reported symptomatic response to CRT and parameters of *systolic* function has consistently been high, there is excellent concordance between the symptomatic response to pacemaker therapy and objective measures of *diastolic* function.

Figure 1. Differential Effects of Altered Cardiac Loading Conditions on Systolic and Diastolic Function in Normal and Myopathic Hearts

(A) Attenuation of improvement in systolic function **(left panel)** and amplification of diastolic dysfunction **(right panel)** in response to altered cardiac loading conditions in systolic heart failure. Changes in left ventricular (LV) diastolic pressure in myopathic and normal ventricles (ΔP and Δp, respectively) for a given change in volume (ΔV), during diastole.
(B) Differential effects of altered cardiac loading conditions induced by pacemaker-mediated atrioventricular interval (AVI) optimization on diastolic versus systolic function. LV inflow velocity is used to characterize diastolic function **(upper panels)**, and left ventricular outflow tract time-velocity integral [LVOT TVI] is used as a surrogate for stroke volume **(lower panels)**. Pacemaker-induced change in loading conditions (an increase in the AVI from 130 to 200 ms) can have a major effect on diastolic function (alteration of LV inflow pattern from *restrictive* to *pseudo-normal*), without any demonstrable improvement in stroke volume. A = atrial component of LV filling, E = early component of LV filling.



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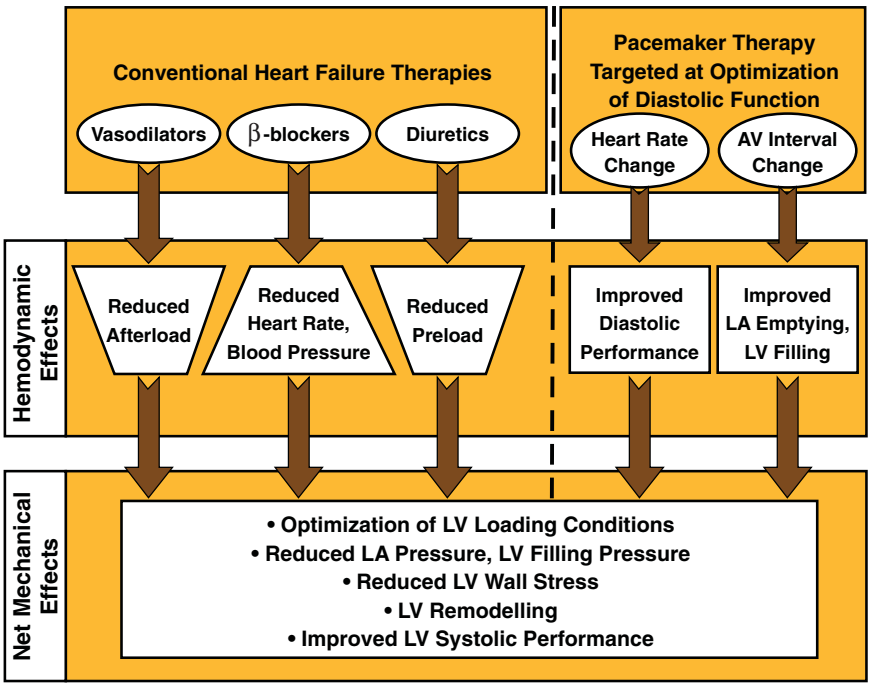
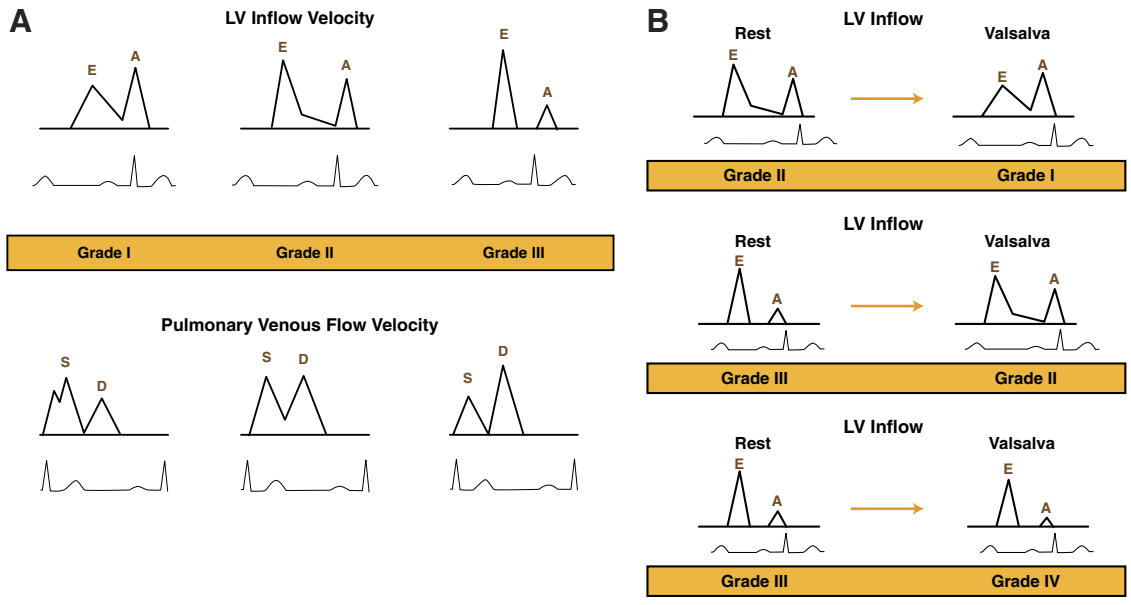


Figure 2. Analogy Between Conventional Heart Failure Therapies and Pacemaker Therapy Targeted at Optimization of Diastolic Function

Conventional therapies which have been shown to improve outcomes in patients with refractory heart failure (vasodilators, β-blockers, diuretics) are modifiers of cardiac loading, analogous to pacemaker-optimization of diastolic function. Reduction of left ventricular (LV) filling pressures reduces LV wall stress, leading to reverse remodeling and secondary improvement of systolic performance. These pacemaker-mediated improvements in cardiac loading may account for many of the benefits associated with cardiac resynchronization therapy. AV = atrioventricular; LA = left atrial.

Figure 3. Doppler Echocardiographic Descriptors of Diastolic Function and Their Response to Pre-Load Reduction

(A) Doppler echocardiographic descriptors of diastolic function. Characteristic LV inflow velocities for the 3 grades of diastolic dysfunction are schematically represented **(upper panels)**, together with corresponding pulmonary venous flow velocity patterns **(lower panels)**. *The responses of these patterns to adjustment of pacemaker settings are used to identify optimal hemodynamics during pacemaker therapy for diastolic dysfunction.*
(B) Effect of instantaneous pre-load reduction, induced by the Valsalva maneuver, on left ventricular (LV) diastolic function. In the **upper panel**, pre-load reduction changes a pseudonormal pattern (*grade II*) to one of impaired relaxation (*grade I*). In the **center panel**, pre-load reduction changes a restrictive filling pattern (*grade III*) to a pseudonormal pattern (*grade II*). If the reduction in pre-load induced by the Valsalva maneuver does not result in a shift from restrictive to pseudonormal filling pattern, the filling pattern is "restrictive irreversible" (*grade IV diastolic dysfunction,* **lower panel**). A = atrial component of LV filling; D = diastolic component of pulmonary venous flow, E = early component of LV filling; S = systolic component of pulmonary venous flow



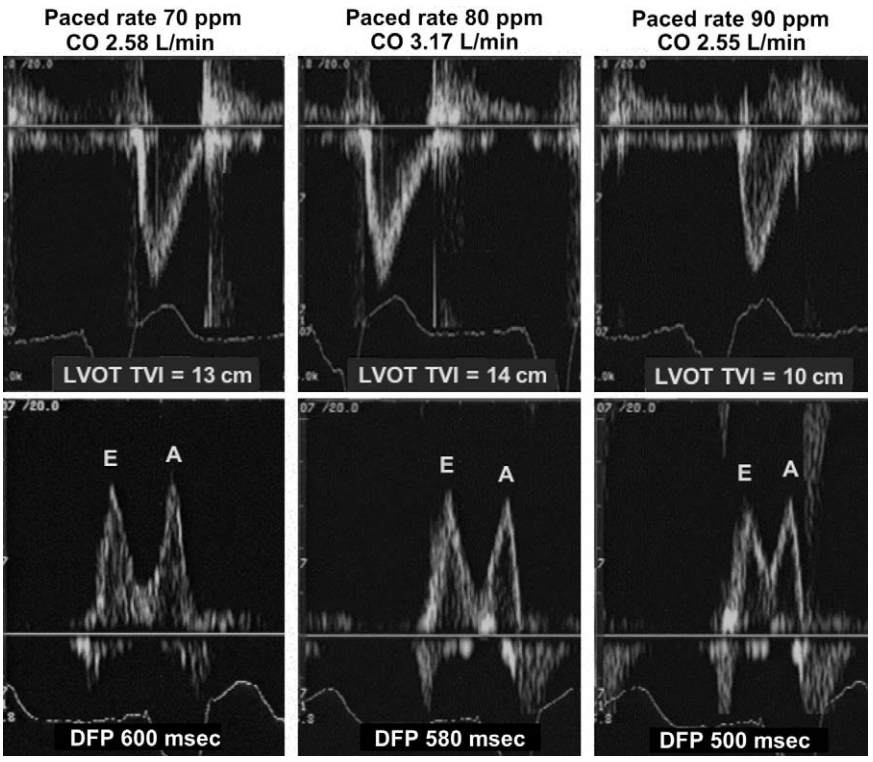


Figure 4. Heart Rate as a Determinant of Diastolic Function

At the initial paced rate of 70 ppm, time-velocity integral across the left ventricular outflow tract [LVOT TVI] was 13 cm **(left upper panel)**; LV inflow showed a pseudonormal pattern, consistent with grade II diastolic dysfunction **(left lower panel)** and cardiac output [CO] was 2.58 l/min. An increase in lower pacing rate to 80 ppm slightly increased LVOT TVI to 14 cm, consistent with a small increase in stroke volume **(center upper panel)**, and an increase in CO to 3.17 l/min, without significant change in diastolic function **(center lower panel)**. When the rate was increased further to 90 ppm, LVOT TVI declined precipitously to 10 cm, consistent with a 29% decrease in stroke volume **(right upper panel)**, and a reduction in CO to 2.55 l/min. This deterioration in systolic function was attributable to a significant reduction in diastolic filling period [DFP] with partial fusion of the early and atrial contributions to LV filling **(right lower panel)** reflecting an increase in left atrial pressure. Symptomatic improvement followed selection of a fixed lower pacing rate of 80 ppm without rate response. A = atrial component of LV filling; E = early component of LV filling.

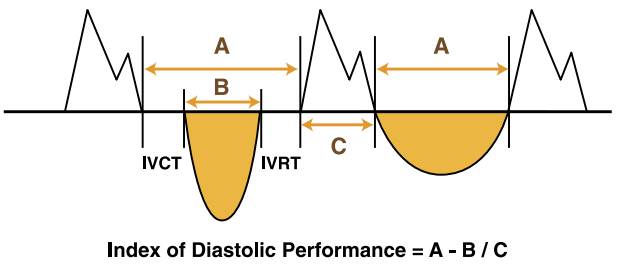


Figure 5. Diastolic Performance as a Determinant of Diastolic Function

Hearts with extremely poor contractile function, in which the isovolumic contraction [IVCT] and relaxation times [IVRT] are inappropriately long, may have a compromised diastolic filling period even in the absence of tachycardia. The *index of diastolic performance* (*IDP*), calculated as the ratio of the sum of isovolumic contraction and relaxation times to diastolic filling period, increases with deteriorating diastolic function. Reduction of the lower pacing rate may produce improvement in diastolic function with symptomatic benefit. A = duration of mitral regurgitant flow; B = duration of LV outflow; C = duration of LV inflow.

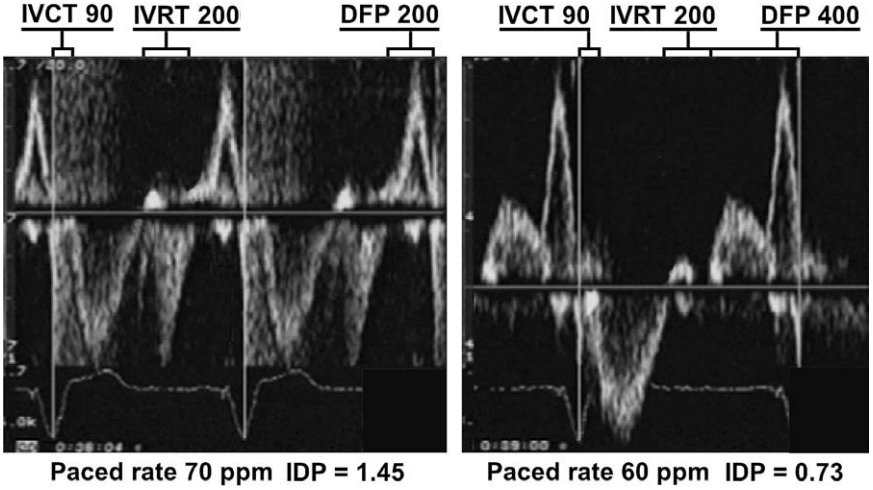
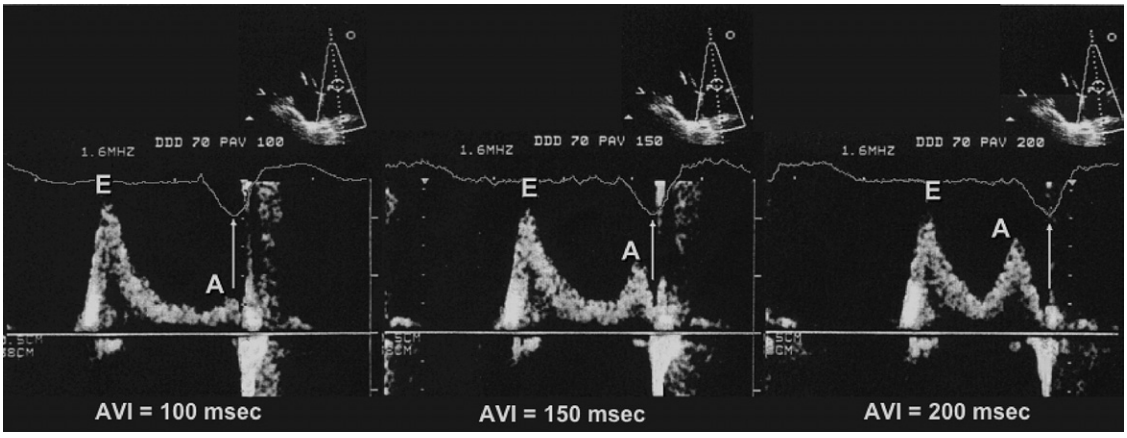


Figure 6. Impaired Diastolic Performance Corrected by Pacemaker Therapy

The beneficial effects of a reduction in the lower paced rate on the index of diastolic performance (IDP) are exemplified in this patient. At the initial paced rate of 70 ppm **(left panel)**, the prolonged isovolumic relaxation time (IVRT) (200 ms) encroaches on the diastolic filling period (DFP) (200 ms), resulting in a "restrictive" filling pattern due to fusion of the early and atrial contributions to LV filling. When the paced rate was reduced to 60 ppm **(right panel)**, DFP increased to 400 ms (a decrease in IDP from 1.45 to 0.73), with improvement in diastolic dysfunction to a grade I pattern. Abbreviations as in Figures 1 and 5.

Figure 7. AV Synchrony as a Determinant of Diastolic Function

Atrioventricular (AV) dyssynchrony is common after dual-chamber pacemaker implantation and its correction is usually associated with significant symptomatic improvement. In this case, at the initial atrioventricular interval [AVI] of 100 ms **(left panel)** the atrial (A) component of left ventricular (LV) filling is barely evident, resulting in a "restrictive filling" pattern. Incremental lengthening of the AVI renders the atrial component of LV filling progressively more apparent. At an AVI of 200 ms **(right panel)**, the LV inflow velocity pattern is consistent with grade II diastolic dysfunction. E = early component of LV filling.



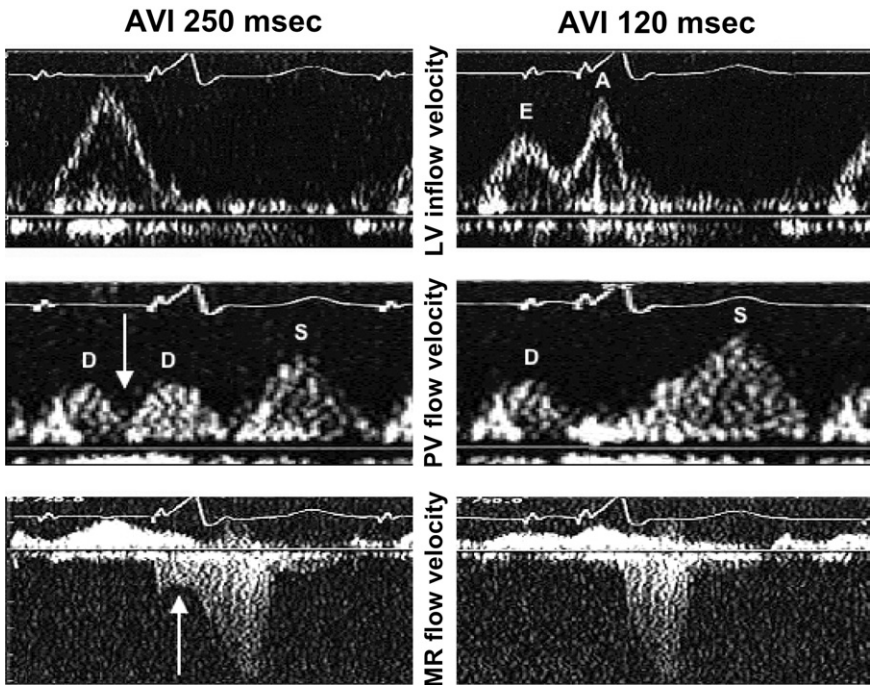


Figure 8. AV Dyssynchrony Due to Excessively Long AVI Corrected by Pacemaker Therapy

In this patient, who had initially reported increased exertional dyspnea and fatigue after biventricular pacemaker implantation, correction of a long atrioventricular interval (AVI) resulted in profound symptomatic improvement. At the initial AVI of 250 ms, a) the early (E) and atrial components (A) of ventricular filling are fused **(left upper panel)**; b) atrial contraction during the early phase of left ventricular (LV) filling interrupts the diastolic phase of pulmonary venous forward flow **(downward arrow, left center panel)**, and the "suction pump" action of atrial relaxation in early systole is attenuated with reduction in the systolic component of pulmonary venous forward flow (S) **(left center panel)**; and c) there is diastolic mitral regurgitation (MR) **(upward arrow, left lower panel)**. At the revised AVI of 120 ms, a) the early and atrial components of ventricular filling are clearly discernible (grade I diastolic dysfunction), implying normalization of left atrial pressure **(right upper panel)**; b) the systolic component of pulmonary venous (PV) forward flow is amplified by return of the "suction pump" action of atrial relaxation in early systole (S) **(right center panel)**; and c) there is no longer diastolic mitral regurgitation **(right lower panel)**.

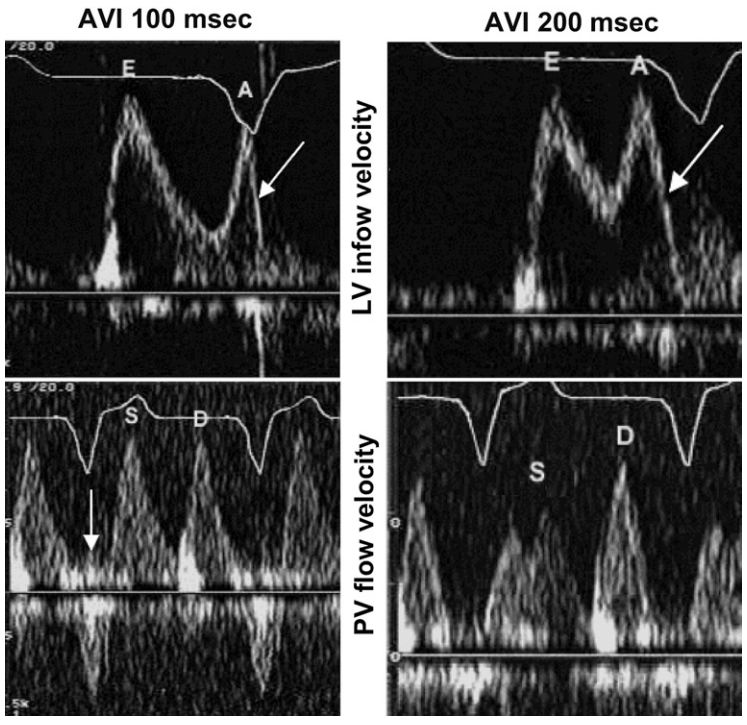


Figure 9. AV Dyssynchrony Due to Inappropriately Short AVI Corrected by Pacemaker Therapy

An inappropriately short atrioventricular (AV) delay may result in atrial contraction that occurs after the onset of ventricular mechanical systole. At the initial atrioventricular interval (AVI) of 100 ms, a) the atrial contribution to left ventricular (LV) filling (A) is truncated by the onset of mechanical ventricular systole, evidenced by rapid deceleration of the A-wave **(arrow, left upper panel)**; and b) the pulmonary vein (PV) Doppler shows "giant P-wave reversal" due to persistence of atrial contraction into the early part of ventricular systole, against a closed mitral valve **(arrow, left lower panel)**. At the revised AVI of 200 ms, a) the atrial contribution to LV filling is completed prior to the onset of ventricular systole, evidenced by slower deceleration of the A-wave **(arrow, right upper panel)**, with change in the LV inflow pattern from a grade II towards a grade I pattern, and b) pulmonary venous flow is normalized. D and S = diastolic and systolic components of PV flow, E = early component of LV filling.

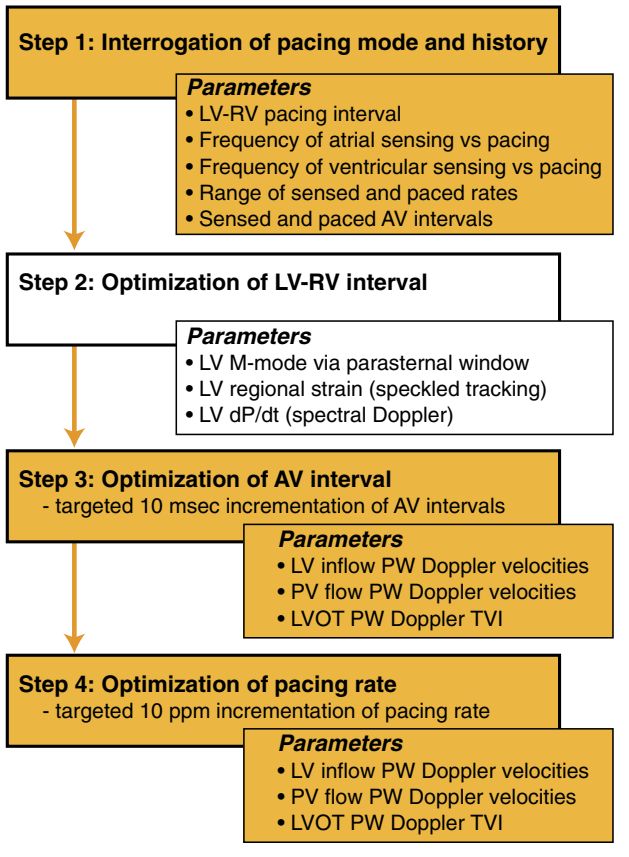


Figure 10. Step-Wise Systematic Approach to Pacemaker Optimization of Systolic and Diastolic Function

PW = pulsed wave; RV = right ventricular; other abbreviations as in Figures 1, 2, and 8.

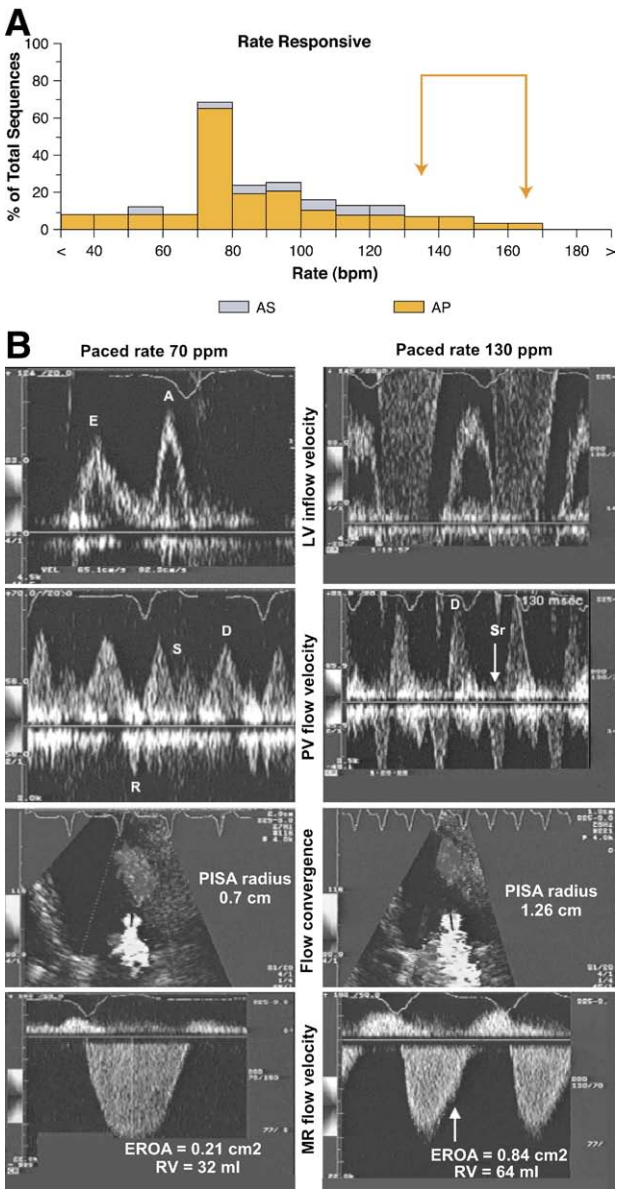


Figure 11. Case Demonstrating Utility of Pacemaker Interrogation for Targeted Pacemaker Therapy in Refractory Heart Failure

(A) Histogram of pacemaker interrogation. The range of documented heart rates (horizontal axis) and the frequency of each rate (vertical axis) are shown. The **yellow-filled portion of each bar** represents the time fraction of atrial pacing (AP), as opposed to atrial sensing (AS) **(grey-filled portion)**. The rate-responsive modality of the pacemaker (DDDR mode), has produced heart rates of at least 130 beats/min for a significant proportion of the time period interrogated **(vertical arrows)**.

(B) Simulation of pacemaker interrogation data. Doppler data were acquired at the lower pacing rate of 70 ppm **(left panels)**, and at a rate of 130 ppm **(right panels)**. **Top panels** show left ventricular (LV) inflow velocities, **second-from-top panels** show pulmonary venous (PV) flow velocities, **lower 2 panels** show flow convergence and mitral regurgitant (MR) flow velocity data used to quantify the effective regurgitant orifice area (EROA) and regurgitant volume (RV) using the proximal isovelocity surface area (PISA) method. At rest, there was grade I diastolic dysfunction with mild-to-moderate MR due to papillary muscle dysfunction. An increase in the pacing rate from 70 to 130 ppm caused severe MR, marked elevation in filling pressure, and rate-limiting exertional dyspnea. Note: 1) Change in LV inflow velocity pattern from grade I diastolic dysfunction at lower rate to fusion of early and atrial components at 130 ppm; 2) loss of systolic components of pulmonary venous forward flow with marked pulmonary venous systolic flow reversal at 130 ppm **(downward arrow, second-from-top right panel)**; 3) increased PISA radius, reflecting increased EROA and RV at 130 ppm **(second-from-bottom right panel)**; 4) rapid deceleration of MR flow velocity at 130 ppm **(upward arrow, lower right panel)**, reflecting development of large left atrial '*v*' wave, due to hemodynamically severe MR. The simple measure of de-activation of the rate-responsive modality (i.e., alteration of pacing mode from DDDR to DDD) produced marked symptomatic improvement. A = atrial component of LV filling; D = diastolic component of pulmonary venous forward flow E = early component of LV filling; R = physiologic pulmonary venous flow reversal during atrial contraction; S = systolic component of pulmonary venous forward flow; Sr = pulmonary venous flow reversal during systole due to severe mitral regurgitation

Pacemaker therapy targeted primarily at parameters of diastolic function may have a much greater role to play in the management of heart failure than has been recognized previously. The degree to which altered ventricular loading conditions induced by improvements in diastolic function might contribute to the long-term benefits of CRT, such as reverse remodeling, has yet to be defined.

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